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What's New in Gastroenterology

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RECENT medical progress in gastroenterology provides an opportunity for a brief commentary on some important new contributions and for a revision or review of older concepts and methods.

As to the present status of therapeutic measures directed toward the cure or control of two diseases —peptic ulcer and chronic ulcerative colitis—it is proper to stress the fact that these diseases still present a challenge, both as to etiology and as to therapy. No cure exists, and general principles still obtain.

Enterogastrone, duodenal extract, and extract of pregnant mare's urine all represent a search for the physiological approach to ulcer therapy. A certain amount of unfortunate publicity has raised as yet unwarranted hopes as to the efficacy of treatment of ulcer by duodenal extract or enterogastrone. To date no convincing evidence has been obtained that duodenal extract is of any striking value in altering the course of peptic ulcer. The bulk of evidence available at present in regard to the use of enterogastrone in the prevention or cure of ulcer leaves little room for enthusiasm. Sandweiss and his group concluded, on the basis of enterogastrone therapy in 42 patients, that clinical results were very disappointing. Symptom-free intervals were short, and recurrences were frequent. These patients were treated for a relatively short period of time, but the experience of others with this product for as long as six months to a year and longer strongly suggests that recurrences are not prevented in a high percentage of cases. The country-wide survey that is being carried out by Ruffin will doubtless be a valuable contribution to this subject. It is to be added that the product is as yet not obtainable in pure form, is irritating and expensive, and cannot be given in doses comparable to those used in early animal experiments.

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The effect of enterogastrone on gastric secretion in normal human beings in doses up to 400 mgm. was negligible in modifying gastric secretion after histamine or Ewald test meals. The use of pregnancy urine extract is not entirely new and is suggested by previous work by Sandweiss and Necheles with urogastrone, a gastrosecretory depressant extracted from human urine. The extract of pregnant mare's urine was used by Page and Heffner on 26 patients with intractable duodenal or jejunal ulcers. This substance has a gastric secretory inhibitory effect in animals and was given as an oral preparation. All other forms of therapy were discontinued during the therapeutic trial over a period of 20 months. Twenty-three of the 26 patients who were properly classified as having intractable ulcers responded favorably during this period of time. All of the chronic jejunal ulcers became asymptomatic within three or four weeks. Obviously such results are encouraging if they can be repeated by other observers and can be shown to be of lasting value.

The use of resins and protein hydrolysates as antacids or buffer solutions requires some comment. It is probably fair to say that in most instances resins offer little or no advantage over other commonly employed preparations. There is no evidence that they have any particular virtue. A careful study on the use of casein hydrolysate by Lopusniak and Berk of Philadelphia demonstrated that casein hydrolysate mixture has a somewhat better buffer and neutralizing action in the stomach than milk or milk and cream but that this buffer action was not significant in the first portion of the duodenum. Furthermore, the use of casein hydrolysate mixture was followed by fairly pronounced secondary stimulation of acid gastric secretion. It would seem that this mixture, except for the very special purpose of providing added nitrogen in badly depleted patients, has little to recommend it over the more orthodox feeding mixtures.

Section of vagal nerves for control of duodenal or jejunal ulcer is still on trial. Reports in the litera-

ture range from enthusiasm to skepticism. Enough time has elapsed to warrant some conclusions, although it is still too early to attempt to make a final evaluation of this procedure. It is fair to say that when performed as a single operative procedure it can be followed by unpleasant symptoms of fullness, gastric stasis, diarrhea, etc., in an appreciable number of patients, although as a rule these symptoms do not persist. Ulcer recurrences following vagotomy alone may run as high as 11 to 12 per cent, a figure that is definitely higher than that of recurrences after subtotal gastrectomy. The combination of posterior gastroenterostomy and vagotomy has received considerable notice, but patients so treated have not been followed for a sufficient period of time to warrant definitive statements. It may be that this type of operation will present a valuable addition to the therapy of ulcer. Certainly it appears to have been a very effective measure in the control of intractable stomach ulcers. It is considered fair, however, to urge conservative skepticism until more time has elapsed. The author's feeling is that vagotomy provides a real addition to the therapeutic armamentarium but that its use probably applies to carefully selected cases and final results following its performance are still not completely known.

Radiation therapy in peptic ulcer has been completely reviewed by Ricketts, Palmer and their associates in Chicago within recent months. This form of treatment is not new, but their report is of interest, inasmuch as it represents observations on more than 800 cases followed during the years 1936 to 1947. The total amount of radiation varied between 1,100 and 2,500 r in divided doses directed toward the fundus of the stomach. Such therapy produced acute transitory inflammation of the gastric wall, with hyperemia, hemorrhage, edema, exudate, and degenerative changes in epithelial cells and lymph follicles. Atrophy of the gastric mucosa often ensued and was uniformly present in patients with prolonged postradiation anacidity. Such irradiation of the acid-secreting portions of the stomach frequently produced achlorhydria, which varied in duration from a few days to as long as eight years. There was a higher incidence of postradiation achlorhydria in patients with gastric ulcer than in those with duodenal or jejunal ulcer. If achlorhydria was produced, ulcer pain disappeared, and if the achlorhydria persisted, there was invariable healing of the ulcer.

The investigators are careful to point out that while roentgen irradiation of the stomach may produce a profound depression of gastric secretion, this depression persisted for variable lengths of time which could not be predicted, nor could the degree of depression be predicted. The effect on the course of the ulcer depended upon the degree and duration of the secretory depression. It is important to note that in those patients with prolonged achlorhydria, gastric atrophy ensued, and it is wise to ask the question whether such an end-result is favorable and whether it might not lay the basis for future difficulties from possible malignant degeneration. It is probable that radiation therapy of peptic ulcer should be employed only in carefully selected cases otherwise resistant to treatment. It should be carried out only by skilled radiologists and should be followed by careful observation. It may represent a proper therapeutic maneuver in certain difficult cases.

The treatment of ulcerative colitis has received constant attention in recent years, but little new has been added. Aureomycin and chloromycetin to date have been tried in small groups of patients, with variable results. It is highly probable that these drugs are an addition of slight importance to the existing measures for attempting to combat colonic infection in this disease. The author's experience with these two preparations has been extremely disappointing.

Experiments indicate that lysozyme production is greatly increased in the diseased colon, but to date no measures have been devised to adequately inhibit lysozyme production or to reduce its activity in removing protective surface mucus. Treatment of ulcerative colitis with extracts of intestinal mucosa has been attempted by Friedman and Haskell of Philadelphia on the theory that there is a deficiency of an intrinsic protective factor or factors normally present in the bowel mucosa. Oral therapy with extract of the small intestine of hogs was tried in a group of patients, with symptomatic improvement in many, as noted by a decrease in frequency of bowel movements and disappearance of gross blood from the stools. Sigmoidoscopic observations also showed decreased mucosal friability, but in patients with widespread disease only a few showed any benefit as evidenced by careful x-ray studies. It is stated that the disease in patients so treated had been refractory to other measures, but such a form of therapy must be followed over a long period of time in this chronic, recurrent malady before a proper evaluation can be made of its effectiveness. It is to be pointed out that one patient had a terrific allergic reaction from the hog mucosa.

A new approach to the treatment of ulcerative colitis is that carried out in a small group of patients by Dennis, Eddy and Westover of Minneapolis, who have reported results of transthoracic vagotomy in 22 patients. Fourteen of these patients showed improvement following this procedure, but the authors are careful to point out that it is an experimental approach and should be so considered until a prolonged follow-up has occurred. It is of interest that in general the good results occurred in patients who had had the disease for only a short time and had minimal bowel scarring.

A very recent report by McDermott, Knight, and Ruiz-Sanches on the use of chloramphenical (chloromycetin) in the treatment of typhoid fever confirms the suggestion of previous reports by Woodard, who used this preparation in Malaya to treat typhoid and typhus. McDermott and his associates report on the treatment of 51 patients with typhoid fever. Four received polymyxin-B, but the drug was rejected because of severe toxicity. Thirty-five patients received

aureomycin in doses of 6 to 12 gm. daily, with uneven and questionable responses. The remaining 13 patients were treated with chloramphenical. In 12 patients the temperature returned to normal in approximately three days, and these patients remained afebrile while being so treated. One of the 13 patients died from a complication while under therapy. It should be pointed out that this remarkable response to the antibiotic was essentially one of a drop in temperature. The drug apparently had no effect on complications of the disease, and studies indicate that it did not reduce the number of typhoid carriers. Nevertheless, if these findings are confirmed, it would seem that an important contribution has been made to the treatment of a hitherto resistant infectious disease.

As to certain recent reports concerning liver disease and its treatment, although the idea is in no sense new, the very careful studies by Kunkel and his associates in New York on the effect of rigid sodium restriction in patients with cirrhosis of the liver and ascites is important because of the completeness of the study. The intake of sodium chloride of less than 1.0 gm. per day in 13 patients with steadily accumulating ascites immediately stopped fluid formation in the abdomen in all but one of the patients, with resulting clinical improvement and an associated rise in serum albumin. When sodium restriction was stopped, ascites returned in all but two of the patients, indicating the necessity of many months of such therapy.

The report by Berger and his collaborators on the effect of an exchange resin (Liquonex CR W) on electrolyte balance and its use in edematous states is of interest in this connection. Oral feeding of this resin resulted in the excretion of 80 per cent of dietary sodium and 70 per cent of dietary potassium in the stool without salt restriction. In a patient with cirrhosis and ascites, the ascitic fluid disappeared in 22 days without the use of other diuretics.

To clarify the role of protein in the treatment of human liver disease, Eckhardt and co-workers studied the effect of protein starvation on the clinical course of the disease and on liver function tests and liver histochemistry. Patients were fed a diet adequate in calories but not sufficient to maintain nitrogen equilibrium. A negative nitrogen balance resulted, but there was manifest clinical improvement, a decrease in liver size, and improvement in laboratory tests. Biopsy studies revealed a diminution of liver cell protein and no alteration in fat content. Resumption of protein feeding in adequate amounts, in addition to an adequate caloric intake, showed progressive histochemical improvement in the liver tissue. It is thus apparent that essential dietotherapy of degenerative liver disease must depend upon an adequate caloric intake and an adequate supply of nitrogen if optimum improvement is to be obtained.

The use of testosterone, choline and methionine was studied by Gabuzda and his group in Boston, who showed that in liver disease, testosterone proprionate had a protein anabolic effect in these patients but that a positive nitrogen balance was most effectively achieved by adequate dietary protein. No appreciable nitrogen-sparing action could be attributed to choline and methionine in generous dosage.

Further evidence that intensive therapy in degenerative liver disease promotes a reversal of serious alterations in liver function is shown in the recent studies of Sterling and his group from Chicago. Electrophoretic studies of serum protein in patients with cirrhosis were followed during intensive therapy. Serious alterations in the level of serum albumin, gamma globulin and and beta globulin fractions were gradually but steadily returned to normal levels in patients who were successfully treated, indicating that these evidences of altered function were not irreversible in many instances.

The use of human albumin has recently been studied by Post and Rose of New York, who administered this substance intravenously to 16 patients critically ill with decompensated cirrhosis for a period of about three months. Sufficient albumin was given to maintain normal serum albumin levels. Careful dietary measures were carried out at the same time, a fact which may well have contributed to the favorable results that were obtained. The authors noted striking improvement in 13 patients. Seven patients who showed pronounced diuresis were comatose when albumin therapy was begun. Rose and Post, unlike some other investigators, feel that intravenous albumin has a definite place in the treatment of decompensated cirrhosis of the liver. The author's observations in similar cases lead to the belief that this is an entirely correct assumption, although the results from intensive albumin therapy are not predictable in advance.

The use of fat in intravenous nutrition has promise of very great clinical importance. Two groups of investigators have recently presented evidence that specially prepared fat emulsions may eventually be available for intravenous therapy, a need that has long been felt. Stare and his group in Boston have amplified previous reports on the use of intravenous fat emulsions in rats and dogs by a very recent statement that within the past year, fat emulsions have been given successfully to human beings, furnishing as much as 1,000 to 1,500 calories by vein daily. Stare states that fat emulsions can be prepared which can be given intravenously without reaction and which contribute appreciably to caloric intake, without requiring large fluid volumes or prolonged infusion times. Studies by Chaikoff, Enteman and Dauben recently reported from the University of California similarly justify the conclusion that emulsified fat introduced directly into the blood stream is available for caloric purposes. These investigators showed that about 50 per cent of tagged injected fatty acids were recovered in the liver and had been incorporated into phospholipids at the end of 24 hours. Further elaboration of this idea should be of inestimable value in providing a means for the rapid control of serious malnutrition provided emulsions can be prepared which can be given without the danger of serious reactions or fat em-

bolism. At present, important studies are being carried out in relation to this particular problem by several other important investigative groups.

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QUESTIONS AND ANSWERS

DR. CHESTER JONES: The first question: "What about the cabbage juice diet for peptic ulcer recently reported upon from Stanford University?"

The proper answer would be—I don't know. It seems to me that the only attitude one can take is that this is an approach to the problem which has not been fully explored, and it is not known exactly what would be the answer. However, it is fair to say the cabbage juice is a glycogen and can cause goiter. Therefore, any such mechanism, if indulged in any length of time, should be watched with a good deal of interest, and also suspicion.

Question: "How do you treat uncomplicated duodenal ulcer? How strict a diet, and what medication?"

As time is limited, I will simply say I think the general principle that we all agree to, as far as medical treatment of uncomplicated duodenal ulcer, is about as follows: It is in two parts, first, treating of the ulcer, and then an attempt in between remissions, to either lengthen the interval of remission, or to prevent it completely. In most cases, physicians are not successful in completely preventing all remissions. In the acute phase, the indicated advice is frequent small meals of simple food. Time is a common denominator of all dietary measures. All one has to do is look at the details of the region to know that the actual food that is used, by and large, is not so important as the fact it is given frequently, on time, and in small amounts.

If the ulcer is very acute and very difficult to control, it means feedings during the night, as well as during the day; or, if one desires—and as a rule I don't—one can put the patient on nasal drip of continuous milk feeding, or provide continuous suction during the night to take away the night secretion. Those are measures that are usually not needed. A simple trick sometimes is to wake the patient up about 1 o'clock in the morning and have a feeding at that time.

How strict a diet? Very strict during the acute phase of several weeks. In between, I think any simple, well-cooked tender food eaten on time, at frequent intervals, five or six feedings a day, should be the proper dietary control for an ambulatory patient whose ulcer is not active at that particular moment.

I think there has been too much attention paid to the very minute details of diet, to the exclusion of a lot of other factors. Anything that contributes to peace of mind and avoidance of physical fatigue is obviously important. It requires knowing the person, and it takes more than a four-minute interview to accomplish that. It takes time.

As to the use of drugs: There is no specific drug that cures ulcer; no specific drug that gives you absolute assurance of the control of the ulcer problem. There are three approaches in the main, however. One is the anti-acid, and I think probably at present in most instances the aluminum gel compounds are good. The thing to do is to avoid that which causes constipation and bowel difficulty in the individual.

The second approach is that of desedation, I think, and very frequently during the acute phase of ulcer, desedation with barbiturates is helpful at times in combination with the use of atropine or its derivatives in order to produce a block on the end of the parasympathetic nerve ending of the stomach.

There is no substitute known among the new drugs to replace belladonna and atropine. The new drugs have proved ineffective in most instances. Furthermore, they are more expensive, and therefore, as a rule, have little to recommend them.

Belladonna is probably as good as any of the antispasmodics, only if given in adequate dosages. At times this does produce side effects, however, to preclude its use. During acute phases of ulcer, parenteral administration of atropine and sodium luminal by the clock, at eight-hour intervals for two or three days, often will get the situation under control. No medication in between recurrences absolutely prevents recurrences. The use of anti-acids certainly does not prevent recurrences.

Question: "Would you say something more about vagotomy, particularly in association with gastroenterostomy to obviate stasis in the stomach?"

I would like to say this: In trying to evaluate the original procedure, it was, I think, very much wiser to do vagotomy only in order to see what vagotomy produced. Simple vagotomy was done on a good many patients who had a certain amount of unrecognized or barely recognized pyloric obstruction. In those cases the operation was a complete failure. If you are going to use vagotomy alone, it is important to make sure there is no real partial obstruction near the pylorus, no matter how little it is. To obviate this, gastroenterostomy has been of real value.

In the intractable case that has been carried for a long time, this approach may be a really valuable one. But I'm sure that we haven't followed these cases long enough as yet. Grimson, who has done a good many at Duke, hasn't followed his cases long enough to be able to say that the recurrence rate is satisfactory. It seems to me that vagotomy should be watched closely, and that the number of cases in which the operation is done should not be increased until we know what a little bit longer observation will tell us. After all, it took us a good many years to find out the end result of gastrostomy, and it has taken us a good many years to find out what the end result of subtotal gastrectomy is. It seems the subtotal gastrectomy is still the method of choice.

Question: "How is it possible to treat a patient with cirrhosis and ascites with a high caloric, high protein diet, and yet keep the sodium intake low enough to prevent recurrence of ascites or edema?"

It simply takes the help of a well-trained dietitian to know how to estimate sodium in foods, and one who is capable of giving the patient some variety. It can be done. It requires care of the patient, and a certain amount of time. It isn't easy, but with good dietary advice one can get the information for the planning of such a diet.

Question: "Do you recommend nutritional supplements of B complex for chronic hepatic insufficiency?"

No. Although on the basis of all the facts that are in I'm not convinced that these are unnecessary, I do know that when one stresses supplements, almost always the patient turns to the supplements because they're easy to take in an adequate diet. One cannot get along on a fairly adequate diet and the use of supplements. The diet has got to come first. The emphasis has got to be placed there, and it has got to be continuous.

Furthermore, we have shown by careful studies on a group of patients using serol liver, that we can apparently get situations in which actually as good results are obtained by diet and rest alone. Rest is important. It cuts down the body requirement. It is just as good as when we added supplements and/or vitamins.

A really adequate diet which contains, I think in these cases, about 2 grams of protein and probably between 40 and 50 calories per kilogram of body weight contains all of the vitamins in that diet. It also contains perfectly adequate amounts of methionine and choline. Additions of

methionine and choline probably do not add enough to warrant their use. That is a personal opinion. I can't prove that last statement entirely, but I strongly suspect it is true on the basis of observations.

On the question of the needle biopsy—Dr. Womack brought out the points this morning, but I think it's only fair to state that some of us have done many hundreds of needle biopsies. If done by somebody who is trained to do it carefully, so the risk of the procedure, which is real but not large—it is a fraction of 1 per cent—is minimized, this method can give adequate information. Cecil Watts in Minneapolis any number of times has taken needle biopsies of the liver. About 3 centimeters in diameter, they show a good deal of the structure. It is always open to question, but in a diffuse disease, such as the condition we call cirrhosis of the liver, I'm sure it can be done.

The practical use of this measure is very valuable for study of the physiological condition. As far as the practical aspect in individual cases is concerned, there are only a few cases out of a large number in which one does do an accurate diagnosis. As Dr. Womack said yesterday, there are certain cases—for example, of painless jaundice—in which exact diagnosis is not possible. Every once in a while, it's important to know whether you're dealing with hepatitis or stasis in the bowel. There are various diseases that involve the liver which are not absolutely identifiable by ordinary laboratory tests, and frequently they can be elucidated by a good liver biopsy.

Question: "Repeat the name of the diuretic for diverting sodium in the gastrointestinal tract."

Liquonex. It is a trade name. It has just been reported in some work reported the first of last week at Atlantic City.